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Heart Failure and Anemia in Sub-Saharan Africa:
Etiology, characterization, prognosis and the role of oral iron -
Experiences from Tanzania

by

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*To my sons Aggrey, Alvin,
Alphonse, my wife Domitila and
my parents*

Heart Failure and Anemia in Sub-Saharan Africa: Etiology, characterization, prognosis and the role of oral iron - Experiences from Tanzania.
THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Background

Heart failure remains unexplored in sub-Saharan Africa. Comorbidities such as anemia and iron deficiency are common and associated with increased mortality. Oral iron supplementation may be feasible in heart failure in countries with limited health care resources.

Objectives

1. To describe the contemporary etiology, clinical characteristics, prognosis and prognostic predictors in patients with heart failure in Tanzania.
2. To determine the prevalence, correlates and prognostic implications of anemia and iron deficiency in patients with heart failure in Tanzania.
3. To compare patients with heart failure in Tanzania and Sweden, with regard to (1) clinical characteristics and utilization of heart failure therapy and (2) prognosis and its predictors.
4. To determine if 90 days of a fixed-dose oral iron sulphate supplementation on top of standard therapy in patients with heart failure and iron deficiency results in an improvement in serum ferritin and other hematological and cardiovascular parameters.

Study I

Etiology, clinical characteristics and prognosis in Tanzanian heart failure patients

The Tanzania heart failure (TaHeF) study was a prospective observational study conducted at Jakaya Kikwete Cardiac Centre of the Muhimbili National Hospital in Dar es Salaam, Tanzania. Patients ≥ 18 years of age with heart failure defined by the Framingham criteria were included and the main outcome measure was all-cause mortality. The study comprised 427 patients of whom 217 (51%) were females and the mean (standard deviation) age was 55 (17) years. Heart failure etiologies included hypertension (45%), cardiomyopathy (28%), rheumatic heart disease (12%) and ischemic heart disease (9%). The mortality rate, 22.4/100 person-years of observation over a median follow-up of 7 months, was independently associated with presence of atrial fibrillation, hazard ratio (HR) 3.4 (95% confidence interval [CI] 1.6-7.0); in-patient status, HR 3.2 (95% CI 1.5-6.8); anemia, HR 2.3 (95% CI 1.2-4.5); pulmonary hypertension, HR 2.1 (95% CI 1.1-4.2); creatinine clearance, HR 0.98 (95% CI 0.97-1.00); and lack of formal education, HR 2.3 (95% CI 1.3-4.2).

Study II

Prevalence and prognostic implications of iron deficiency and anemia in heart failure in Tanzania

The design and patient material were the same as in study I. The main outcome measure was a composite of time to hospitalization for heart failure or death. The prevalence of anemia was 57%. The overall prevalence of iron deficiency was 49% distributed as 69% vs. 21% in subjects with and without anemia ($p < 0.001$). The one-year survival free from a composite of hospitalization for heart failure or death was 70%. The presence of iron deficiency anemia increased the likelihood for outcome measure (HR 2.67, 95% CI 1.4-5.1). Anemia without iron deficiency did not influence the risk.

Study III

Characteristics and prognosis of patients with heart failure in Tanzania and Sweden

This was a prospective study in which the patients from the TaHeF study (Study I) were compared with patients from the Swedish heart failure registry (SwedeHF). Patients from TaHeF (n=427) and SwedeHF (n=51,060) were initially compared in unmatched cohorts. Another comparison was made after matching 1:3 by gender and age ± 5 years (TaHeF n=411 vs. SwedeHF n=1232). The primary outcome was time to all-cause mortality. In the unmatched cohorts the TaHeF patients were younger (age [interquartile range; IQR] 55 [40-68] vs. 77 [64-84] years; $p<0.001$) and more commonly women (51 vs. 40%; $p<0.001$). The three-year survival was 61% in both cohorts. In the matched cohorts, TaHeF patients had more hypertension (47 vs. 37%; $p<0.001$) and more anemia (57 vs. 9%; $p<0.001$). Their left ventricular ejection fraction (LVEF) was more frequently preserved and heart failure more advanced and of longer duration. Beta-blockers were less frequently used in Tanzania. The crude mortality was worse in TaHeF (HR 2.25, 95% CI 1.78-2.85; $p<0.001$) with a three-year survival of 61 vs. 83%. However, following multivariable adjustment, the risk was similar (HR 1.07, 95% CI 0.69-1.66; $p=0.760$). In both cohorts, preserved LVEF was associated with higher mortality than reduced LVEF in the crude but not in the adjusted analyses.

Study IV

Oral iron improves serum ferritin in patients with heart failure and iron deficiency: A single-arm clinical trial within the Tanzania heart failure study

This was a prospective, single-arm clinical trial which included patients aged ≥ 18 years with stable symptomatic (NYHA II-IV) heart failure, hemoglobin 8-15g/dL, and iron deficiency, defined as serum ferritin level <100 ng/mL or 100-299 ng/mL with concurrent transferrin saturation $<20\%$. Oral ferrous sulphate was administered at dose of 200 mg three times per day during 90 days. A total of 237 patients were screened of whom 102 met inclusion criteria (54% males; mean age \pm SD 58 ± 16 years). In 97 patients who completed follow-up, the mean (\pm SD) ferritin level improved from 123 ± 70 ng/mL at baseline to 255 ± 143 ng/mL after 90 days of treatment ($+107\%$; $p<0.001$), hemoglobin from 11.7 ± 2 to 12.3 ± 2 g/dL ($+5\%$; $p<0.001$), 6MWT distance from 543 ± 148 to 574 ± 166 meters ($+6\%$; $p<0.001$), LVEF from 37.8 ± 12.2 to $44.5 \pm 10.7\%$ ($+17\%$; $p<0.001$) and NT-proBNP from 986 ± 774 to 582 ± 503 ng/L (-41% ; $p<0.001$).

Conclusions

Patients with heart failure in Tanzania were younger than their counterparts from the developed world. Hypertension was the leading cause of heart failure in Tanzania, unlike in Sweden and other developed countries where ischemic heart disease is predominant. This calls for the need for early detection and treatment of hypertension. Even after age and gender matching, patients in Tanzania had more severe heart failure and worse crude but similar adjusted prognosis. Independent and modifiable predictors of mortality were anemia, atrial fibrillation and lack of education. Iron deficiency anemia, common in Tanzanian heart failure patients, was independently associated with a poor prognosis. Oral iron supplementation was sufficiently absorbed to replenish serum ferritin in Sub-Saharan patients with heart failure. It was associated with improved hemoglobin, 6MWT distance, LVEF and NT-proBNP.

LIST OF ORIGINAL PAPERS

This thesis is based on the following papers to which will be referred by their roman numbers

- I. Makubi A, Hage C H, Lwakatare J, Kisenge P, Makani J, Rydén L, Lund LH.
Etiology, clinical characteristics and prognosis of patients with heart failure in Sub-Saharan Africa. The Tanzania heart failure prospective study.
Heart. 2014;100(16):1235-41
- II. Makubi A, Hage C H, Lwakatare J, Mmbando B, Kisenge P, Rydén L, Lund LH, Makani J.
Prevalence, correlates and prognostic implications of anemia and iron deficiency in Tanzanian patients with heart failure: A report from the TaHeF study.
Heart. 2015;101(8):592-9
- III. Makubi A, Hage C H, Ulrik S, Lwakatare J, Janabi M, Kisenge P, Dahlström U, Rydén L, Makani J, Lund LH.
Comparative characterization and prognosis in the Tanzania heart failure (TaHeF) study and the Swedish heart failure registry (SwedeHF).
International Journal of Cardiology. 2016;220:750-758
- IV. Makubi A, Lwakatare J, Mmbando B, Hage C H, Janabi M, Kisenge P, Rydén L, Makani J, Lund LH.
Oral iron improves serum ferritin in patients with heart failure and iron deficiency: A prospective trial within the Tanzania heart failure study (TaHeF-iron deficiency).
Manuscript

LIST OF ABBREVIATIONS

6MWD	Six-minute walk distance
FAIR-HF	Ferinject® Assessment in Patients With IRon Deficiency and Chronic Heart Failure
JKCI	Jakaya Kikwete Cardiac Institute
MNH	Muhimbili National Hospital
MUHAS	Muhimbili University of Health and Allied Sciences
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
STAMINA-HeFT	The Study of Anemia in Heart Failure Trial
sTfR	Soluble transferrin receptor
SwedeHF	Swedish Heart failure Registry
TaHeF	Tanzania Heart Failure study
TSAT	Transferrin saturation

INTRODUCTION

HEART FAILURE

Heart failure definition

The diagnostic criteria for heart failure are complex. Traditionally the definition of heart failure was based on a combination of symptoms and physical signs of fluid retention as e.g. in the Framingham Heart Study criteria, which are 100% sensitive and with a specificity of 78%¹. Due to advances in diagnostic facilities, the definition of heart failure has been updated as can be seen in management guidelines issued by international cardiac societies. According to the European Society of Cardiology², the diagnosis requires the fulfillment of three or more conditions (Table 1a). In this guideline, the term heart failure is used to describe the symptomatic syndrome, graded according to the New York Heart Association (NYHA) functional classification based on symptoms and signs (Table 1b).

Table 1. Diagnosis of heart failure (a) and NYHA class based on symptoms and signs (b)			
a.		b.	
The diagnosis of HF-REF requires three conditions to be satisfied:		NYHA class	Explanation
1. Symptoms typical of HF		I	No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations.
2. Signs typical of HF		II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
3. Reduced LVEF			
The diagnosis of HF-PEF requires four conditions to be satisfied:			
1. Symptoms typical of HF		III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
2. Signs typical of HF			
3. Normal or only mildly reduced LVEF and LV not dilated			
4. Relevant structural heart disease (LV hypertrophy/LA enlargement) and/or diastolic dysfunction		IV	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased.
HF = heart failure; HF-PEF = heart failure with ‘preserved’ ejection fraction; HF-REF = heart failure and a reduced ejection fraction; LA = left atrial; LV = left ventricular; LVEF = left ventricular ejection fraction. Signs may not be present in the early stages of HF (especially in HF-PEF) and in patients treated with diuretics.			

Epidemiology

Heart failure is a worldwide public health problem that affects millions of people and carries a poor prognosis. The global prevalence of heart failure is estimated to be over 23 million people^{3,4}. The heart failure prevalence and incidence are 3% and 0.5% in developed countries, increasing with age^{1,3,5}. The corresponding proportions in Sub-Saharan Africa are unknown. However, the available data based on hospital studies indicate that heart failure is the commonest cardiovascular condition and accounts for about 15-20% of deaths among Africans admitted to hospitals^{6,7}. Heart failure is assumed to account for over 30% of admissions to cardiovascular units and 3-7% to general internal medicine wards in Africa⁸.

The pattern of cardiovascular disorders in Africa is becoming indistinguishable from those in developed countries⁹, with more people reaching middle and older ages as one explanation. Still in the few studies from Sub-Saharan Africa, the gender distribution appears equal but age is lower than in developed countries¹⁰⁻¹².

Etiology

Large observational studies e.g. the Acute Decompensated Heart Failure National Registry (ADHERE) in the United States of America (USA) and Euro Heart Failure Survey II (EHFS II) in Europe have provided a greater insight into the etiology of patients with heart failure in developed countries^{13,14}. In these populations, ischemic heart failure alone or in coexistence with hypertension, atrial fibrillation and diabetes constitute the commonest causes of heart failure, with dilated cardiomyopathy in a minority^{13,15}. Despite this present understanding, the pattern of heart failure etiology is still evolving. The causes of heart failure and demographics are not uniformly distributed and great geographic variance exists. The picture seems more complex in Africa even if detailed information on this subject is limited. Historically, the main etiologies of heart failure in Sub-Saharan Africa have been rheumatic heart disease and cardiomyopathies¹⁶, but there may be a change towards a pattern more similar to that in the developed world^{12,17-19}. The few available contemporary observational studies from Sub-Saharan Africa show that hypertension and idiopathic cardiomyopathies are main causes of heart failure in a significantly younger group of patients when compared to those in developed countries^{19,20}. Furthermore, myocardial infarction is becoming progressively more important with the adoption of western lifestyles and an ageing population²¹.

Therapy

During the past decades, clinical trials have provided valuable information of importance when managing heart failure patients²²⁻²⁵. Current guidelines advocate the use of angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, mineralocorticoids receptor antagonists, diuretics and devices (implantable cardiac resynchronization therapy and cardioverter-defibrillators)^{2,26}. Still, evidence from developed countries shows that the adherence to the guideline recommendations, at least in some respects, is sub-optimal²⁷⁻²⁹. Little is known regarding the treatment practices of heart failure in Sub-Saharan Africa. The Sub-Saharan Africa Survey of heart failure (THESUS-HF) registry reported on three important observations regarding the management of heart failure. First the use of aspirin was frequent in patients with non-ischemic heart failure, while the combined use of the hydralazine and nitrate, shown to be effective in patients of African descent³⁰, was hardly used at all, while beta-blockers were only prescribed to about 50% of heart failure patients²⁰.

Prognosis

Despite available therapy, the prognosis of heart failure remains poor^{4,14,31}. The Framingham study suggested that the one and five year survival rates were a remarkable 57% and 25% in men and 64% and 38% in women³². The ADHERE, EHFS II and the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With heart failure (OPTIMIZE-HF) registries showed an in-hospital mortality of 3.8-6.7%^{13,14,33}. With regards to long-term outcomes, OPTIMIZE-HF reported 8.6% mortality after 90 days³³.

The limited data from Sub-Saharan Africa show a similar in-hospital mortality in the magnitude of 3.8% and 4.2% in the Nigerian acute heart failure and THESUS-HF registries^{20,34}. The similarity in in-hospital mortality in reports from the developed countries and Africa is of interest considering the demographic and etiological differences between these parts of the world.

ANEMIA

Anemia definition

The World Health Organization (WHO) defines anemia as hemoglobin <13.0g/dl in men and <12g/dl in women³⁵ categorized as mild (hemoglobin 10-11.9 g/dl for women and 10-12.9 g/dl for men), moderate (hemoglobin 7-9.9 g/dl for both genders) or severe (hemoglobin <7 g/dl for both genders³⁶.

Anemia as an important comorbidity in heart failure

Evidence based therapy management of heart failure remains difficult in the presence of comorbidities that contribute to the pathophysiology and progression of the underlying cardiac disease^{37,38}. Anemia, a frequent and important co-morbidity in refractory heart failure³⁹, is potentially amenable to intervention⁴⁰.

The prevalence of anemia increases with worsening NYHA functional class and varies depending on the studied patient population and the hemoglobin level used to define anemia. This explains why it ranges widely between 4% to 55% in various studies^{2,41,42} in developed countries. In the EHFS II⁴³, which included 115 hospitals from 24 countries, 18% of male patients were anemic (defined as a hemoglobin <11g/dl), a prevalence that would have been 33% if the hemoglobin threshold had been increased to 12.0 g/dL. Thus, a 1.0 g/dL increase in the hemoglobin threshold nearly doubled the proportion of anemic patients in the same study cohort.

The information on the presence of anemia in a Sub-Saharan Africa heart failure population is limited (Table 2) compared to the large number of studies of this topic performed in developed countries. Using the WHO cut-off, the scattered information reveals that the prevalence of anemia in heart failure in Sub-Saharan Africa ranges from 14-64% (average = 45%), to be compared with 36% in the general Sub-Saharan Africa population⁴⁴.

Pathophysiology of anemia in heart failure

The causes of anemia in heart failure are not well known. Anemia may be associated with iron, folate, or B12 deficiency, renal failure or other comorbidities including anemia of chronic disease and dilutional anemia⁵⁰.

Table 2. Studies in Sub-Saharan Africa in heart failure reporting anemia in adults			
Authors, country and year	Sample size	% Anemia	Definition of anemia by hemoglobin or packed cell volume
Ogah <i>et al</i> , Nigeria, 2014. ³⁴	452	8.8	<10g/dl
Damasceno <i>et al</i> , 9 African countries, 2012 ¹²	1006	15.2	<10g/dl
Stewart <i>et al</i> , South Africa, 2008. ¹⁹	699	10.0	Male, <11g/dl, female <10 g/dl
Karaye <i>et al</i> , Nigeria, 2008. ⁴⁵	79	41%	Packed cell volume <39% in male and <36% in female
Kuule <i>et al</i> , Uganda, 2009. ³⁶	157	64.3	Male, ≤12.9g/dl, female, ≤11.9g/dl
Inglis <i>et al</i> , South Africa, 2007. ⁴⁶	163	13.5	WHO
Dzudie <i>et al</i> , Cameroon, 2008.	140	15.7	Not available
Oyoo <i>et al</i> , Kenya, 1999. ⁴⁷	91	13.2	Not available
Ojji <i>et al</i> , Nigeria, 2013. ⁴⁸	475	8.0	Not available
Onwuchekwa <i>et al</i> , 2009. ⁴⁹	423	6.2	Not available

Iron deficiency

Iron is essential for cell growth, electron transport reactions, transport of oxygen, oxidative phosphorylation and for the function of some enzymes⁵¹. Iron deficiency has been considered clinically important only in the presence of anemia. However, iron deficiency impairs aerobic performance regardless of the presence of anemia⁵², suggesting its role to be considerably more complex. Two biochemical forms of iron deficiency have been described. The first is absolute deficiency, which is characterized by depletion of iron available in the circulation (bound to transferrin) and iron stores (ferritin in the liver and iron in the reticular endothelial system). This may be caused by poor dietary intake, chronic blood loss due to surgery, use of aspirin/non-steroidal anti-inflammatory drugs leading to gastritis/peptic ulcer disease, uremia, gastrointestinal malignancies or to increased iron demand as e.g. during pregnancy^{53,54}. The second form is functional iron deficiency in which there is a depletion of transferrin bound iron available in the circulation although the body storage of iron is adequate. This is partly due to blunted erythropoiesis induced by inflammation⁵⁵ and elevated hepcidin levels by sequestration of iron in macrophages, resulting in hypoferremia⁵¹. Hepcidin binds to the cellular iron export channel ferroportin causing its internalization and degradation thereby decreasing iron efflux from iron exporting tissues into plasma. By this mechanism, hepcidin inhibits dietary iron absorption, the efflux of recycled iron from splenic and hepatic macrophages, and the release of iron from storage in hepatocytes^{51,56}. With either of the two forms of iron deficiency, and regardless of the hemoglobin level, both oxygen delivery and utilization are impaired in myocardial and other cells^{57,58}.

Anemia of chronic disease

Anemia is often associated with chronic inflammatory and malignant disorders, as well as renal failure, and it has become increasingly recognized in heart failure. Cytokines such as tumor necrosis factor-alpha and interleukin-6 are elevated in heart failure and are associated

with the catabolic and dysmetabolic state seen late in the disease⁵⁹. Increased erythrocyte sedimentation rate and levels of the acute phase reactants C-reactive protein (CRP) and ferritin are seen^{50,60}. In patients with anemia and heart failure, iron can be absent in bone marrow stain, the gold standard for iron deficiency. However, in these patients, CRP is elevated and ferritin is not suppressed, as would be expected in iron deficiency, suggesting that inflammation may nevertheless play a role⁶¹. Moreover, studies are ongoing to establish the exact role of hepcidin, a protein synthesized by the liver, which plays a major role in iron metabolism. Hepcidin synthesis is suppressed by anemia, hypoxia and erythropoiesis, and induced by inflammation⁵⁶. Inflammatory cytokines, such as interleukin-6 IL-6, increase the synthesis of hepcidin, resulting in anemia of inflammation. In a study by Matsumoto et al.⁶², serum hepcidin-25 concentrations were regulated by iron storage and erythropoiesis but not by IL-6 in heart failure patients with anemia suggesting that that anemia of inflammation a minor cause of anemia in heart failure.

Use of angiotensin converting enzyme inhibitors

Angiotensin converting enzyme inhibitors may cause anemia and are indeed used to treat erythrocytosis. They reduce the hematocrit following renal transplantation and may induce or contribute to anemia in heart failure⁶³.

The cardiorenal syndrome

Chronic and progressive renal failure and associated anemia is common in heart failure (Figure 1). The term the “cardiorenal syndrome” has been used, but a clear definition does not exist. Renal failure in heart failure may be secondary to hypoperfusion and hypoxia, but also to venous congestion and inflammation. Impaired nutrition, decreased bone marrow perfusion and side effects from heart failure drugs may also contribute to both renal failure and anemia^{64,65}.

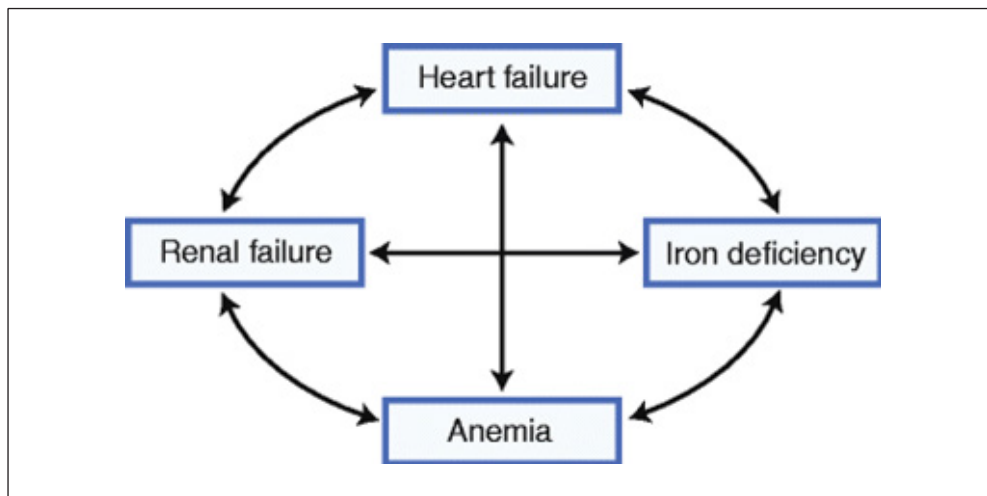


Figure 1. The cardiorenal anemia iron-deficiency syndrome may interact in a way that one exacerbates another

Iron deficiency in heart failure

In 2002, iron deficiency anemia was considered to be among the most important contributing factors to the global burden of disease⁶⁶. Surveys in Tanzania estimated that 30-55% of the adult population is anaemic⁶⁷⁻⁶⁹ and the prevalence of iron deficiency anemia was estimated to be 40-61%⁷⁰⁻⁷².

Burden of iron deficiency in heart failure

In developed countries the prevalence of iron deficiency in heart failure ranges from 14-73% depending on the study population and which diagnostic criteria that are applied. Corresponding data in Sub-Saharan Africa are scarce (Table 3).

Diagnosis of iron deficiency in heart failure

Various studies have suggested higher levels (60-100 µg/L)^{83,84} of serum ferritin as sufficient for diagnosing absolute iron deficiency in the presence of coexisting inflammation, infection and malignancy, as opposed to the more commonly used serum ferritin cut-off level of <30 µg/L⁸³. Even stricter cut-off values, 12-15 µg/L, have been used⁸⁵ in the absence of inflammation. This is based on the fact that patients with acute or chronic disease usually have elevated levels as a result of intracellular iron accumulation and inflammatory response, serum ferritin being an active phase reactant. Therefore, in heart failure as with other chronic conditions, iron deficiency has been defined in two forms; (1) absolute iron deficiency which is defined as serum ferritin <100ng/ml and (2) functional iron deficiency defined as serum ferritin 100-300 ng/mL and transferrin saturation <20%⁶¹. These criteria have been used in several clinical trials in heart failure⁸⁶⁻⁸⁸.

Table 3. Studies reporting the magnitude of iron deficiency in heart failure

Authors, year	N	% With iron deficiency	Definition of iron deficiency
Jankowska <i>et al</i> , 2014. ⁷³	165	37	Low hepcidin and high sTfR Serum ferritin and TSAT
Rangel <i>et al</i> , 2014. ⁷⁴	127	36	SF<100ug/L or SF 100-299ug/L +TSAT <20%
Parikh <i>et al</i> , 2014. ⁷⁵	574	61	SF<100ug/L or SF 100-299ug/L +TSAT<20%
Enjuanes <i>et al</i> , 2014. ⁷⁶	1278	58	SF<100ug/L or SF 100-299ug/L +TSAT<20%
Ijsbrand <i>et al</i> , 2014. ⁷⁷	1506	50	SF <100ug/L or SF 100-299ug/L +TSAT<20%
Jankowska <i>et al</i> , 2013, ⁷⁸	443	35	SF<100ug/L or SF 100-300ug/L +TSAT<20%
Nanas <i>et al</i> , 2006, ⁶¹	37	73	Bone marrow
Cristina <i>et al</i> , 2006, ⁵⁵	148	36	High soluble TR and /or low TSAT
Cohen-Solal A, <i>et al</i> ⁷⁹	832	72	SF<100ug/L or SF 100-299ug/L +TSAT<20%
Yeo TJ <i>et al</i> , 2014 ⁸⁰	751	61	SF<100ug/L or SF 100-299ug/L +TSAT<20%
De Silva R <i>et al</i> , 2006. ⁸¹	955	29	Lower limit for serum iron and SF
Klaus K. A <i>et al</i> , 2004. ⁸²	296	14	Low SF
Abbreviations. sTfR=Soluble transferrin receptor; TSAT=Transferrin saturation; SF=Serum ferritin; TR=Transferrin receptor.			

Prognostic role of iron deficiency in heart failure

There is limited and partially conflicting information on the impact of iron deficiency on prognosis in heart failure. In most available studies^{74,76,77,89} iron deficiency carried a higher risk of poor outcome in heart failure irrespective of the presence of anemia. In contrast, Parikh et al⁷⁵ found that iron deficiency was not associated with all cause or cardiovascular mortality in patients with self-reported heart failure.

*Intervention studies for iron deficiency in heart failure*Recombinant human erythropoietin

Several agents have been explored as potential therapies for iron deficiency in heart failure. Erythropoiesis stimulating agents such as recombinant human erythropoietin raise hemoglobin and improve functional and exercise capacity and quality of life in heart failure⁹⁰, and in the Study of Anemia in heart failure Trial (STAMINA-HeFT) it was associated with a trend toward lower combined all-cause mortality and heart failure hospitalization⁹¹. However, these agents may be associated with adverse thromboembolic outcomes^{92,93}.

Iron supplementation

Parenteral iron therapy has demonstrated short to medium term benefits in the form of improved symptoms, quality of life measures and reduced hospitalization rates in a number of controlled and uncontrolled clinical trials in heart failure and iron deficiency^{64,86,87,94–96} (Table 4), all conducted in developed countries. In the Ferinject Assessment in Patients with Iron Deficiency and Chronic heart failure (FAIR-HF) study⁸⁶, patients were randomized to i.v. iron or placebo and 50% vs. 28% and 47% vs. 30% reported improved quality of life and NYHA class, respectively. Similarly in the Ferric Iron Sucrose in heart failure (FERRIC-HF) study⁹⁴, 35 patients with heart failure were subjected to 16 weeks of intravenous iron or no treatment in a 2:1 ratio. The NYHA functional class improved in 8 patients (44%) in the iron group versus none of the patients in the control group ($p = 0.03$). I.v. iron for heart failure has not been studied in Sub-Saharan Africa.

Oral iron is an established therapy for treating iron deficiency in a wide range of medical conditions but has not yet been widely tested in heart failure. Preliminary studies on randomized clinical trial on erythropoietin stimulating agents vs. oral iron showed no iron improvement with oral therapy on hemoglobin, exercise and ferritin. However, in a recent, non-randomized clinical trial¹⁰⁶ replenishment of hemoglobin, transferrin saturation (TSAT) and ferritin were similar to with i.v. iron in FAIR trial⁸⁶ in patients with heart failure and preserved left ventricular ejection fraction. A randomized trial¹⁰⁷ also showed that ferritin and hemoglobin increased with both i.v. and oral iron.

CONCLUSIONS

Heart failure continues to remain a substantial burden on the health-care systems and communities in both developed and Sub-Saharan Africa countries. Despite the fact that a lot of progress has been made with regard to our understanding of the natural history of heart failure in developed countries, the picture is more complex in Sub-Saharan Africa and the limited data available have provided little insight on the etiology, comorbidities, treatment, and prognosis.

Anemia and iron deficiency, in isolation or in combination, are important comorbidities in heart failure and confer poor prognosis. Its treatment has been shown to improve the outcome in heart failure patients in developed countries. In Sub-Saharan Africa, the relation between anemia and iron deficiency remains largely unexplored and more information is needed to tackle this increasing public health problem for further development of locally feasible and acceptable interventions.

Table 4. Studies on intravenous iron in heart failure					
Author and reference	Study design	Sample size	Type of i.v. iron	Dose/duration	Benefits
Ben-Assa <i>et al</i> , 2015. ⁹⁷	Uncontrolled	34	Ferric sucrose	200 mg, 6w	↑hemoglobin
Reed <i>et al</i> , 2015. ⁹⁸	Uncontrolled	13	Ferric gluconate	250 mg bd/d, 3d	↑hemoglobin, ↑SF, ↑TSAT
Gaber <i>et al</i> , 2011. ⁹⁹	Uncontrolled	40	Ferric dextran	200 mg/w, 4-8w	↑NYHA, ↑6MWD, ↑SF, ↑TSAT, ↑exercise capacity, ↑renal function, ↑QOL
Usmanov <i>et al</i> , 2008. ⁶⁴	Uncontrolled	32	Ferric sucrose	100 mg 3 times/w, then once/w, 26w	↑hemoglobin, ↑NYHA, ↑LV diameters
Bolger <i>et al</i> , 2006. ¹⁰⁰	Uncontrolled	16	Ferric sucrose	1 g daily, 12d	↑hemoglobin, ↑TSAT, ↑6MWD ↑NYHA
Toblli <i>et al</i> , 2015. ¹⁰¹	Controlled	60	Ferric sucrose	200 mg /w, 5w	↑hemoglobin, ↑SF, ↑TSAT, ↑ LV diameters, ↑LVEF, ↑ CrCl, ↑NT-proBNP
Ponikowski <i>et al</i> , 2014. ⁸⁷	Controlled	304	Ferric carboxymaltose	Total dose 500-2000 mg, in correction phase and 500 mg in maintenance, 52w	↑6MWD, ↑NYHA, exercise capacity, ↑PGA, ↑QoL, ↓ heart failure hospitalization, ↑fatigue score
Terrovitis <i>et al</i> , 2012 ¹⁰²	Controlled	40	Ferric sucrose	300 mg weekly, 6w	↑hemoglobin
Anker <i>et al</i> , 2009. ⁸⁶	Controlled	459	Ferric carboxymaltose	200 mg, 24w	↑hemoglobin, ↑SF, ↑TSAT, PGA, ↑NYHA, ↑6MWD, trend ↓ heart failure hospitalization
Abbreviations: SF=Serum ferritin; TSAT=Transferrin saturation; NYHA=New York Heart Association; 6MWD=Six minute walk distance; QOL=Quality of life, LV=Left ventricular; LVEF=Left ventricular ejection fraction; PGA=patients' global assessment, ↑=improved, ↓=worsened					

AIMS

- To assess the contemporary etiology, clinical characteristics, prognosis and predictors of prognosis in heart failure in Tanzania.
- To determine the prevalence and prognostic implications of anemia and iron deficiency in heart failure in Tanzania.
- To compare patients with heart failure in Tanzania and Sweden, with regard to (1) clinical characteristics and utilization of heart failure therapy, and (2) prognosis and prognostic indicators.
- To determine if 90 days of a fixed-dose oral iron sulphate supplementation on top of standard therapy in patients with heart failure and iron deficiency results in an improvement in serum ferritin and other hematological and cardiovascular variables.

STUDY METHODS

STUDY SETTINGS

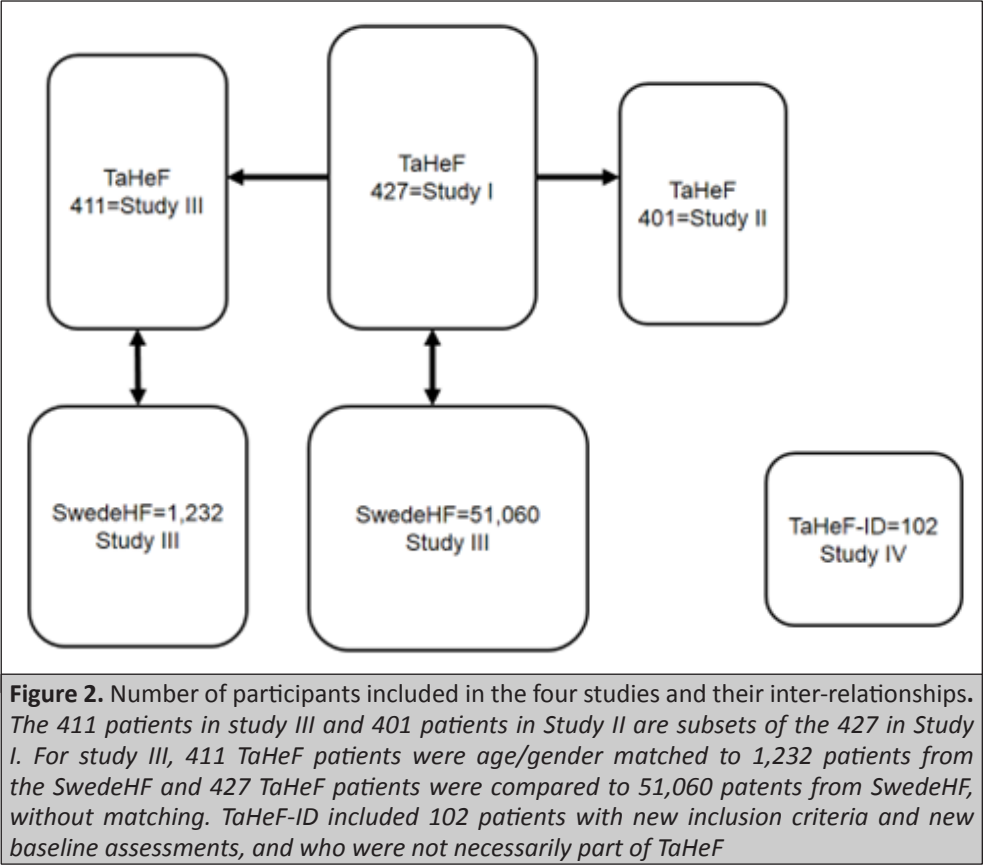
The four studies were conducted at the Jakaya Kikwete Cardiac Institute (JKCI) of the Muhimbili National Hospital (MNH), in Dar es Salaam, Tanzania. This center is a national referral hospital serving all of Tanzania, close to 45 million people. In the third study, patients in TaHeF were compared to patients in the Swedish heart failure Registry (SwedeHF). Figure 2 shows number of patients from the Tanzanian and Swedish cohorts in the different studies.

PARTICIPANTS, DESIGNS, PROTOCOLS AND ENDPOINTS

Study I

Aim

This study aimed to describe the contemporary etiology, clinical characteristics, mortality, and its predictors in heart failure in Tanzania.



Patients

The inclusion criterion in the Tanzania heart failure study (TaHeF) was a clinical diagnosis of heart failure according to the Framingham criteria. Following screening (n=521) in the outpatient clinic and among stable patients in inpatient cardiac wards 427 patients were recruited for the study. Exclusion criteria were age <18 years and declining to participate.

Study design and protocol

TaHeF was a prospective cohort study. At baseline, data from the patient history and physical examination and laboratory/imaging studies were collected. Descriptive data included fifty demographic, social, heart failure clinical, co-morbidity, laboratory (MNH Central Pathology Laboratory) and echocardiography variables. The underlying probable cause of heart failure was clinically determined through a combination of case history, hospital records, physical examination, chest X-rays, ECG and echocardiographic recordings. Criteria for hypertensive heart failure, rheumatic heart disease, and cardiomyopathy were modified according to the chronic heart failure cohort in the Heart of Soweto Study¹⁹, according to definitions listed in Table 5.

Endpoints

The outcome measure for study I was all-cause mortality. Patients were followed in the outpatient clinic on a monthly basis. Follow-up via clinic visits and phone contact were maintained until August 2013. Patients who could not be reached were censored alive at the last confirmed contact or considered lost to follow-up if no contact was made after enrollment. In patients who died outside of MNH, date of death was obtained from next of kin.

Table 5. Criteria for defining heart failure etiological conditions	
Probable heart failure etiological condition	Criteria
Hypertensive heart failure	Clinical heart failure according to the Framingham criteria and documented history of Hypertension and at least one of the followings; increased LV, septal thickness (≥ 1.3 mm), diastolic dysfunction, LV systolic dysfunction
Ischemic heart failure	Clinical heart failure according to the Framingham criteria and results of non-invasive (e.g. ECG and abnormal regional wall motion on echocardiography) or invasive tests when available (for purposes of TaHeF, performed abroad) with LV ejection fraction $\leq 45\%$
Heart failure due to idiopathic dilated cardiomyopathy	LV ejection fraction $\leq 45\%$ and possibly LVEDD ≥ 55 mm of indeterminate origin
Rheumatic heart failure	heart failure secondary to primary underlying rheumatic heart disease with moderate to severe cardiac valvular dysfunction (e.g. regurgitation or stenosis)
Peripartum cardiomyopathy	Heart failure secondary to left ventricular systolic dysfunction (LV ejection fraction $\leq 45\%$) towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found. The left ventricle may not be dilated
Other heart failure etiologies	Includes congenital heart disease with e.g. hypertrophic cardiomyopathy, restrictive cardiomyopathy, endomyocardial fibrosis, and heart failure secondary to HIV infection, tuberculosis or chronic lung disease

Study II

Aim

To determine the prevalence, correlates and prognostic implications of anemia and iron deficiency in patients with heart failure in Tanzania.

Patient selection

Patients in study I (n=427) were selected for study II with additional exclusion of those who were lost to follow up or lacked information on hemoglobin. The final population consisted of 411 patients.

Study design and protocol.

This was the same as in study I.

Dependent variables and endpoints

The primary dependent variable was anemia at baseline and the secondary dependent variable was a composite outcome of time to hospitalization for heart failure or all-cause mortality (whichever came first). The index date was defined as date of outpatient visit or date of hospital. Based on the WHO criteria, anemia was defined as a hemoglobin <13 g/dl for males and <12 g/dl for females and graded as mild for levels between 10.0-12.9 g/dl (males)/11.9 g/dl (females), moderate for a hemoglobin level between 7.0-9.9 g/dl and severe if <7 g/dl. Serum iron markers were not available and iron deficiency was therefore defined as a mean corpuscular volume (MCV) of <80 femtolitres (fL) [16]. Subsequently, the iron deficiency and anemia status of each participant was allocated into one of the following four categories: 1) Anemia no, iron deficiency no = absence of anemia + MCV \geq 80 fL; 2) Anemia no, iron deficiency yes = absence of anemia + MCV <80 fL; 3) Anemia yes, iron deficiency yes = presence of anemia + MCV <80 fL; and 4) Anemia yes, iron deficiency no = presence of anemia + MCV \geq 80 fL

Study III

Aim

To compare characteristics and prognosis of heart failure in TaHeF vs. SwedeHF.

Patients

Study III included the TaHeF patients in study I. SwedeHF provided the study population for comparison with regards to clinical characteristics, therapy, prognosis, and predictors of prognosis. This ongoing nationwide registry was initiated in 2000¹⁰⁸. For the purpose of the present study, patients registered from May 11, 2000 to December 31, 2012 and followed until December 31, 2012 were included.

Design and protocol

TaHeF and SwedeHF are both prospective cohorts where analyses for purposes of this comparison were conducted retrospectively. The SwedeHF protocol, case report form and annual reports are available at <http://www.swedehf.se>. Patients were compared overall (n=427 from TaHeF vs. 51,060 from SwedeHF) and after matching 1:3 by gender and age \pm 5 years yielding n=411 vs. n=1,232. All patients in TaHeF and SwedeHF were considered for matching except those who a) were lost to follow-up in TaHeF (n=16); and b) patients in both populations with missing echocardiographic information (n=18 and n=8,281, respectively).

Endpoints

The index date was defined as the date of outpatient visit or date of hospital admission in TaHeF and hospital discharge in SwedeHF. The outcome was time from index date to all-cause mortality. In TaHeF, patients were followed in the outpatient clinic on a monthly basis as in studies I and II. In SwedeHF date of death was obtained from the population registry and patients alive were censored at the time for the last follow-up, December 31 2012.

Study IV*Aim*

The aim was to test the hypothesis that 90 days of a fixed-dose oral iron sulphate supplementation on top of standard therapy in patients with heart failure and iron deficiency results in an improvement in serum ferritin and other hematological and cardiovascular parameters.

Patients

Study IV was conducted two years after TaHeF and included both surviving patients from TaHeF and new heart failure patients above the age ≥ 18 years. Patients were required to have stable symptomatic (NYHA II-IV) heart failure (regardless of EF) based on symptoms and signs, at least one echocardiography abnormality from Table 1 and NT proBNP >300 ng/L, hemoglobin 8-15 g/dL and iron deficiency defined as: serum ferritin level <100 $\mu\text{g/L}$ or 100-299 $\mu\text{g/L}$ with concurrent transferrin saturation $<20\%$. Exclusion criteria were age <18 years; pregnant/lactating women; known stage III-IV liver disease; known stage III-IV HIV disease; known malignancy; evidence of active bleeding; known allergy or intolerance to iron tablets; already receiving or having an indication for iron supplementation; malabsorption condition or other condition other than heart failure suspected to interfere with iron absorption; having received blood transfusion in the last 4 weeks; known hemolytic anemia; known folate/B12 deficiency; and consent not provided.

Protocol

Following enrollment, all patients entered a three-month treatment period with open-label oral iron. During this period, patients were followed by monthly clinic visits. Iron therapy consisted of oral ferrous sulphate (film coated tablets) at dose of 200 mg administered three times daily for three months. Criteria for early termination were: patient unable to tolerate treatment or developed an anaphylactic reaction.

Endpoints

The primary outcome was the mean change in serum ferritin level from baseline to three months after oral iron initiation. Secondary outcomes included mean changes in hemoglobin, NT-proBNP, left ventricular ejection fraction (LVEF) and the six-minute walk test (6MWT) distance.

PROCEDURES AND LABORATORY TESTS**Echocardiography**

For all studies for Tanzanian patients, echocardiography was performed with General Electric Vivid 5 with a 2.5-5 MHz probe. LVEF was measured by the 2D Biplane Simpson technique and agreed by consensus between two senior cardiologists at MNH. In SwedeHF, LVEF was determined according to local protocol at each participating site.

Hematological measurements

For all studies at MNH full blood profiles were obtained by means of a hematology analyzer (Beckman Coulter ACT5 DIFF). In SwedeHF the corresponding profiles were performed at local accredited laboratories.

Biochemical analyses

Blood samples for all biochemical tests were drawn from an antecubital vein, collected in two tubes (a total of 10 ml) that immediately were put in ice and centrifuged within 20 minutes. Biochemical tests (serum ferritin, serum iron, transferrin saturation and creatinine) were performed using Cobas Integra 400 Plus Chemistry Analyzer (Roche, Basel, Switzerland) while creatinine was analyzed by the use of a Chemistry Analyzer (Roche Cobas Integra 400 plus) at the National Central Pathology Laboratory at MNH. Serum NT-proBNP levels were analyzed at the central pathology laboratory of MNH with enzyme immunoassay for the quantitative determination (Biomedica Medizinprodukte GmbH & Co KG, Vienna, Austria) using BIOTEC ELISA Reader (ELx800). In SwedeHF laboratory data were analysed according to accredited methods at local participating sites.

Six-Minute walk test

In study IV 6MWT was conducted by a single operator in a 30 m marked indoor corridor, following the American Thoracic Society guidelines (10). The Borg scale was recorded at baseline and six minutes.

All investigations performed at baseline (except ECG) were repeated at the three-month follow-up visit in study IV. Moreover, all investigator-judged adverse events during the three-month follow-up period were recorded. Patients were also urged to report possible adverse effects of iron replacement, such as abdominal cramps, constipation, heartburn, nausea, and vomiting, which were also recorded.

STATISTICAL METHODS

Descriptive statistics

Data in TaHeF were entered into an electronic case report form built in the OpenClinica software (<https://www.openclinica.com/>) and via a web-based case report form (eCRF) into a database managed by the Uppsala Clinical Research Center (UCR, Uppsala, Sweden) in SwedeHF. Continuous variables were tested for normality distribution using normal probability plots and reported as mean \pm standard deviation or median (interquartile range) if data distribution was skewed. Categorical variables were summarized using frequencies and percentages. The influence of selected, clinically relevant characteristics on outcomes was assessed by Kaplan-Meier plots. Analyses were performed using stata version 13 and R statistical packages. A two-sided p-value of 0.05 was considered statistically significant.

Analytical statistics

Study I

Univariate and multivariate Cox proportional hazards regression analyses were used to assess the association between baseline variables and mortality during follow-up. Criteria for entry into the multivariate model were clinical relevance (age and gender) or p-value ≤ 0.10 in univariate analysis. Patients who were lost to follow-up (16 of 427) were excluded

from survival analyses and patients who had missing data (57 of 411 patients on follow-up) were excluded from multivariate analysis, leaving 354 patients included in the multivariate analysis.

Study II

The association between selected baseline characteristics and survival free from a composite of hospitalization due to heart failure or all-cause mortality was assessed by Kaplan-Meier plots. Univariate and multivariate logistic regression analyses were used to determine the association between baseline variables and presence of anemia at baseline as a dichotomous variable, while Cox regression was used to determine the association between anemia and iron deficiency and the composite endpoint. In the multivariate analysis all variables with p-value <0.10, and in addition age, sex and heart failure causes, were included. Additional restricted cubic spline models at three knots were used to determine the linear effect quantitative variables on primary and secondary outcomes. Patients who were lost to follow-up (16 of 401) were excluded from the analyses of the composite outcome. Analyses were adjusted for potential modification effects of sex, LVEF, site of recruitment and NYHA class. Interaction terms between exposure categories and potential effect modifiers were created and assessed for significance in the multivariate models using a likelihood ratio test, estimates of the associations being stratified by the variable of interest.

Study III

For baseline description of clinical characteristics, continuous variables were reported as median (interquartile range) and compared using Mann-Whitney U-test while categorical variables were compared by means of the chi-square test. The risk of heart failure in TaHeF vs. in SwedeHF, overall and by heart failure with preserved EF (HFpEF; defined as EF \geq 40%) and reduced EF (HFrEF; defined as LVEF <40%), was assessed in Kaplan-Meier analyses and univariable Cox regressions. Adjustment for clinically relevant confounders was made by multivariable Cox regressions. The interaction between cohort and selected clinically relevant baseline pre-defined sub-groups and the hazard ratios in these sub-groups were assessed in multivariable Cox regressions and displayed in a forest plot. Furthermore, the association between selected baseline variables and mortality was assessed by multivariable Cox regressions separately in the matched TaHeF and SwedeHF populations. Missing data was handled by multiple imputations (n=10), imputed separately in the SwedeHF and TaHeF populations.

Study IV

The sample size calculation was based on a 100% increase from baseline in mean serum ferritin based on Beck-da-Silva et al ¹⁰⁷. A minimum of 89 patients would be required to reach this increase with a standard deviation of the mean differences of 250 ng/mL, using a 2-sided alpha of 0.05 with 90% power. Considering a possibility of 15% dropout rate, the sample size was set to 102. Paired analyses with the use of t-test or Wilcoxon matched pairs test where appropriate were performed on primary and secondary measures before and after iron supplementation. Pre-specified subgroup analyses of the primary endpoint were performed in relation to: NYHA class, presence or absence of anemia based on the WHO definition ¹⁰⁹ and heart failure with preserved EF (HFpEF; defined as EF \geq 40%) vs. heart failure with reduced EF (HFrEF; defined as LVEF <40%)¹¹⁰. The relation between the baseline serum ferritin and percentage change in ferritin concentration was assessed using linear regression.

ETHICAL CONSIDERATIONS

All studies conformed to the declaration of Helsinki. The TaHeF study was approved by the ethical review board of the Muhimbili University of Health and Allied Sciences (MUHAS). Permission to conduct the study was obtained from MNH. All patients provided written informed consent. The establishment of the SwedeHF registry was approved by a multisite Ethics Committee. Individual patient consent was not required, but the patients were informed of entry into national registries and allowed to opt out. Permission to access data for the purpose of study III was provided by the SwedeHF steering committee and a separate ethics approval was obtained for this study within SwedeHF.

RESULTS

Selected baseline clinical characteristics for participants included in TaHeF studies I-III are presented in Table 6, which also includes the corresponding comparison population from SwedeHF for study III.

STUDY I

Among 427 included patients in TaHeF (Table 6 and Figure 2), 217 (51%) were females and the mean (standard deviation) age was 55 (17) years. A majority of patients had formal education (80%), were outpatients (63%) and were either in NYHA class III or IV (71%).

Etiologies of heart failure

Among 388 patients who had echocardiography examination, heart failure etiologies included hypertension (45%), cardiomyopathy (28%), rheumatic heart disease (12%), ischemic heart disease (9%), TB related pericardial disease (2%), HIV related cardiomyopathy (1%) and endomyocardial fibrosis (0.5%) (Figure 3).

Comorbidities in heart failure

Pulmonary hypertension (Pulmonary HT) was present in 17% of patients, atrial fibrillation in 16%, diabetes in 12%, and clinically significant anemia in 12% (Figure 4). Mean LVEF was $41 \pm 12\%$ and 62% of patients had an LVEF $<45\%$.

Prognosis and its predictors

During follow up, 66 patients died, resulting in a mortality rate of 22.4 per 100 person-years of observation. The overall six-month survival rate was 90%.

The multivariate predictors of mortality (Figure 5) were atrial fibrillation, hazard ratio 3.4 (95% confidence interval 1.6 to 7.0); in-patient status 3.2 (1.5 to 6.8); anemia, 2.3 (1.2 to 4.5); pulmonary hypertension, 2.1 (1.1 to 4.2); lower creatinine clearance, 0.98 per unit increase (0.97 to 1.00) and lack of formal education, 2.3 (1.3 to 4.2).

STUDY II

A total of 401 heart failure patients (Figure 2) (median age 56 [IQR 41-67]) years were included. Selected baseline characteristics are presented in Table 6.

Prevalence of anemia and iron deficiency

The prevalence of anemia was 57% (Figure 6). The prevalence of iron deficiency was 49% distributed as 69% vs. 21% in subjects with and without anemia (p-value <0.001). Normocytic anemia was observed in 18% of the patients while none had macrocytic anemia.

Factors associated with anemia in heart failure

The risk of having anemia was positively associated with residency outside Dar es Salaam (OR 1.72; [95% CI 1.02 – 2.89]; $p=0.038$), atrial fibrillation (4.12 [1.60 – 10.61]; $p=0.003$), LVEF $<45\%$ (2.70 [1.57 – 4.67]; $p<0.001$) and negatively (ORs per unit decrease) with creatinine clearance (0.98 per unit increase [0.97 – 0.99]; $p=0.012$) and total cholesterol (0.78 per unit increase; [0.63 – 0.98]; $p=0.029$).

Table 6. Baseline characteristics of study participants

Continuous variables are presented as median (interquartile range [IQR]) and categorical variables as numbers (%) if not otherwise stated

Variable	TaHeF Study I n=427		TaHeF Study II n=401		SwedeHF Study III n=51,060 Unmatched Compared vs.TaHeF_study_I (n=427) Matched Compared vs.TaHeF (n=411)			
	n/median	%/IQR	n/median	%/IQR	n/median	%/IQR	n/median	%/IQR
<i>Social demographics</i>								
Age (years)	55	41-68	55	41-67	77	68-84	55	41-67
Males	210	49			30,871	60	612	50
Formal education	337	80	318	79	51,060	100	1,232	100
<i>Clinical</i>								
In-patient	117	27	112	30	30,665	60	581	47
Heart failure duration ≥6months	287	67	70	67	25,491	50	478	39
NYHA class III-IV	342	79	320	80	14,882	43	308	32
<i>Pharmacological treatment</i>								
ACEi/ARB	393	92	393	92	40,691	80	1,110	90
Beta blockers	177	42	177	41	42,352	84	1,088	89
Loop diuretics	374	88	350	82	40,926	81	811	66
Aldosterone antagonist	308	72	308	72	14,258	28	357	29
Digoxin	165	39	165	39	8,795	71	187	15
Hydralazine	19	4	19	4				
Statins	33	8	33	8	21,683	42		
Aspirin	109	26	109	26				
Clopidogrel	21	5	21	5				
Antiretroviral therapy	10	2	10	3				
Warfarin	11	3	11	3	18,408	36	406	33
<i>History of invasive treatment</i>								
Valve intervention					2,787	6	69	6
Revascularised					12,277	24		
Cardiac resynchronisation therapy					1,014	20		
Implantable cardioverter defibrillator					1,278	26		
<i>Physical examination</i>								
Body mass index (kg/m ²)								
<20	19	4	17	4	2,666	12	63	10
20-25	208	49	197	49	8,186	38	203	32
26-30	119	27	110	27	5,784	27	182	29
>30	81	20	77	19	5,175	24	187	29
Heart rate (beats/min)	88	72-104	88	73-104		72	64-83	
Blood pressure (mmHg)								
Systolic	132	28	132	28	127	110-140	120	109-135
Diastolic	84	16	84	16	70	65-80	73	65-80
LV ejection fraction (%)	40	32-48	40	32-47				
Creatinine clearance (ml/min)	68	49-89	67	48-89	56	39-81		
Hemoglobin (g/L)	119	106-132	119	106-132	132	119-144		
NT-proBNP (ng/L)					2,651	1,130-5,870		

Abbreviations. NYHA=New York Heart Association; ACEi= An angiotensin-converting-enzyme inhibitor; ARB=Angiotensin receptor blocker; NT-proBNP=N-terminal pro B-type natriuretic peptide.

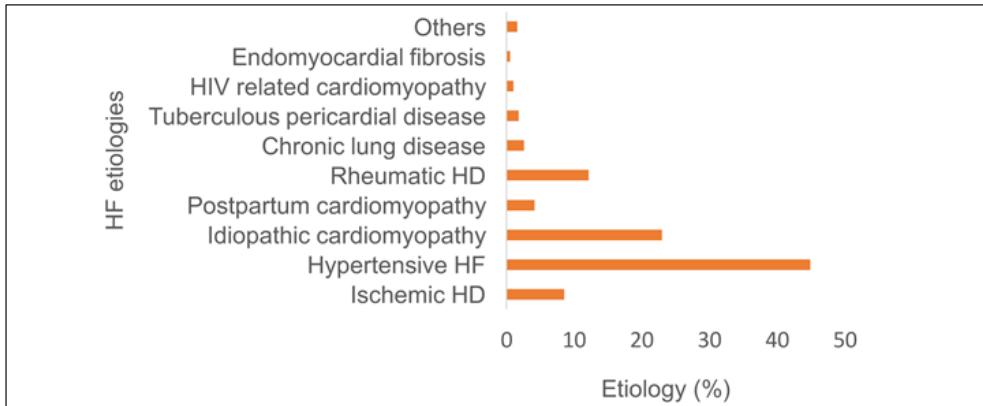


Figure 3. Etiologies of heart failure in TaHeF

Others, hypertrophic cardiomyopathy (0.7%); restrictive cardiomyopathy (0.5%); and adult congenital disease (0.3%); HD, heart disease.

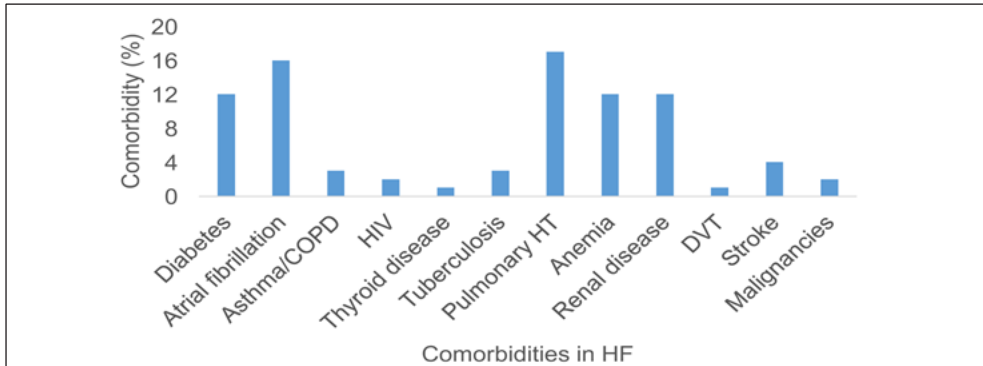


Figure 4. Prevalence of comorbidities in heart failure

COPD=chronic obstructive pulmonary disease, HT=hypertension, DVT=deep venous thrombosis

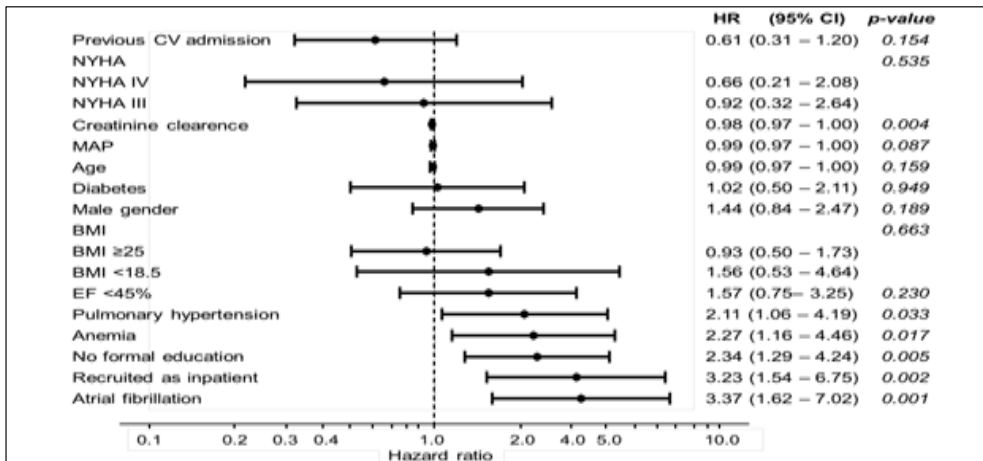


Figure 5. Predictors of mortality in heart failure in TaHeF

Abbreviations. CV=Cardiovascular, NYHA=New York Heart Association; MAP=Mean arterial pressure; BMI=Body Mass Index; EF=Ejection fraction.

Prognostic associations between iron deficiency, anemia, and the composite endpoint

The one-year survival free from a composite of hospitalization for heart failure or death from any cause was 70%. After adjustment of a number of confounders, the presence of iron deficiency anemia increased the risk (HR 2.67; 95% CI 1.39 – 5.07; $p=0.003$), while anemia without iron deficiency or iron deficiency without anemia did not influence the risk.

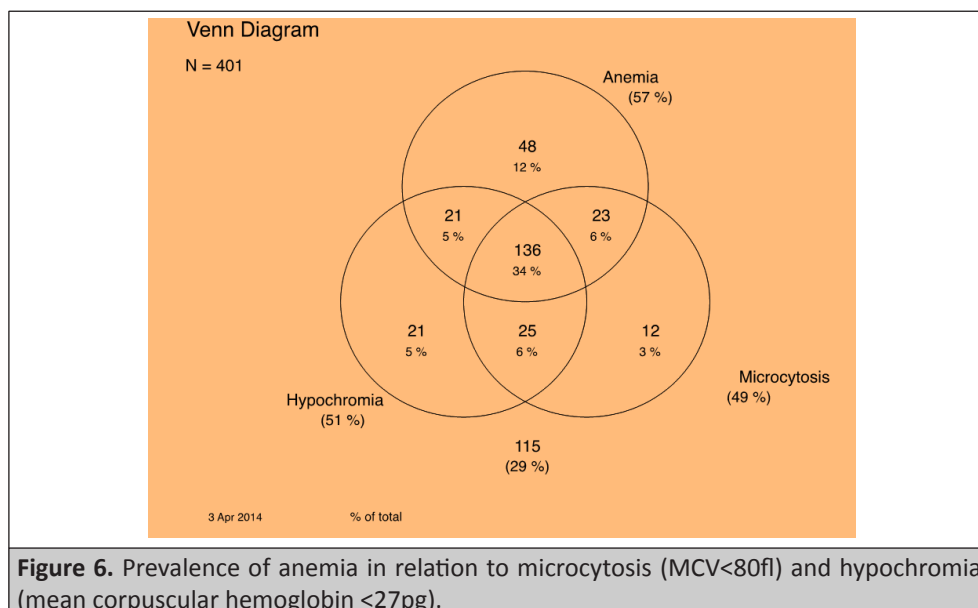
STUDY III

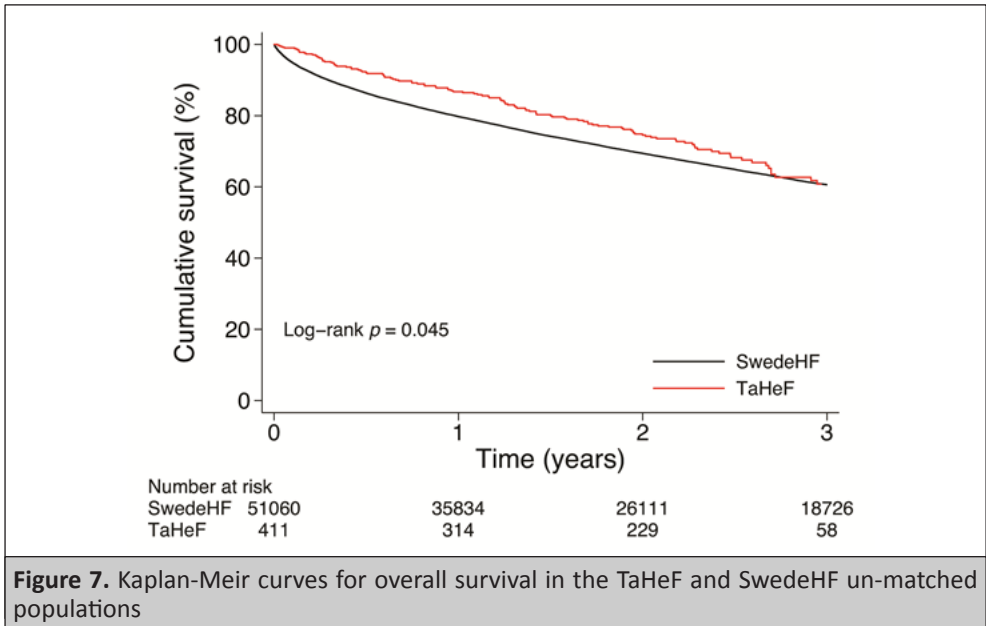
Patients included for the overall unmatched comparison of TaHeF ($n=427$) vs. SwedeHF ($n=51,060$) and for the matched cohorts of TaHeF ($n=411$) vs. SwedeHF ($n=1232$) are shown in Figure 2. Selected baseline characteristics for unmatched and matched SwedeHF cohorts are presented in Table 6.

Fifty one per cent of TaHeF patients were women and median age was 55 ([IQR] 40-69) year while a majority of the Swedish patients were men (60%; $p<0.001$) and the median age was significantly higher than in TaHeF, at 77 (64-84) years ($p<0.001$).

Unmatched cohorts

There were, as expected, numerous demographic and clinical differences in both the overall and matched cohorts. TaHeF patients had a lower level of the following: education, LVEF, body mass index (BMI) (Table 6), prevalence of ischemic heart disease, atrial fibrillation, diabetes mellitus and pulmonary disease. The prevalence of hypertension was similar while NYHA class was more advanced and the prevalence of anemia was higher while the use of beta-blockers was lower in the TaHeF population in which there was no use of revascularization, cardiac resynchronization therapy (CRT) or implantable cardioverter defibrillator (ICD). Despite the much higher age in SwedeHF, the survival up to 3 years was only minimally greater in TaHeF and at three years, it was similar at 61% in both overall cohorts (Figure 7).

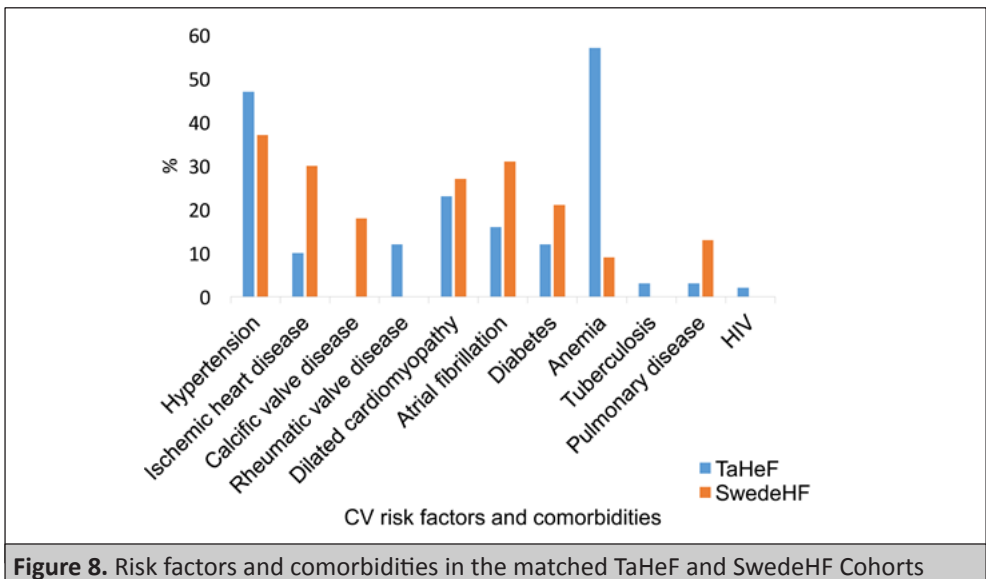




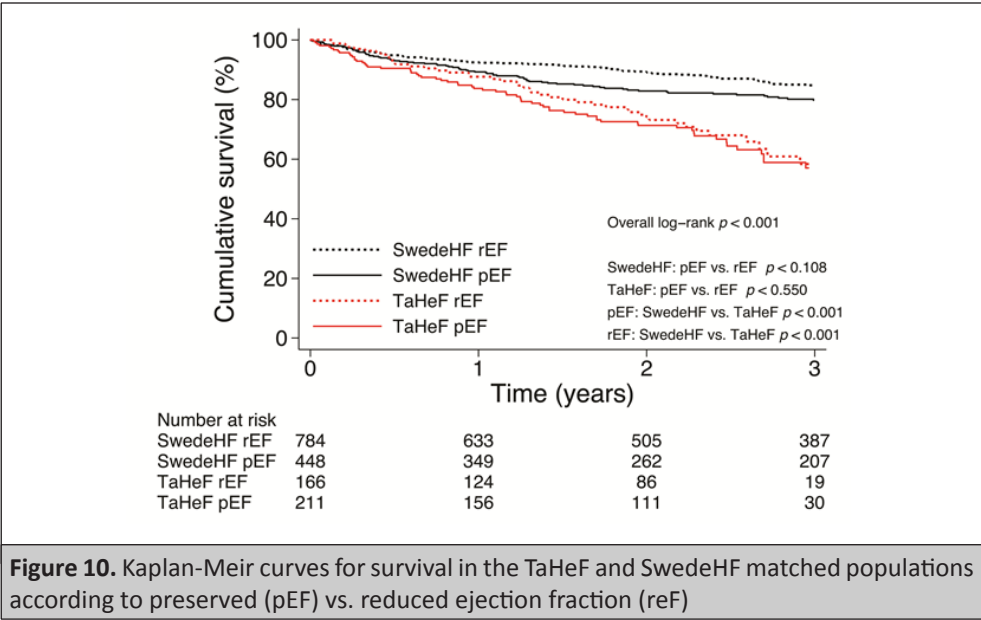
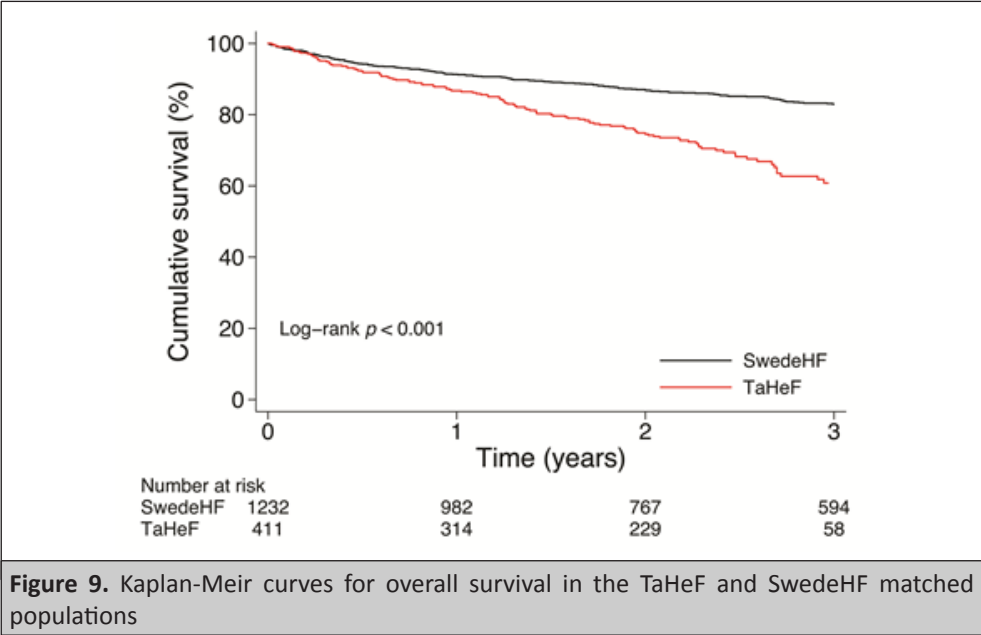
Matched cohorts

TaHeF patients had more hypertension (47% vs. 37%, $p < 0.001$), more anemia (57% vs. 9%), more preserved LVEF, more advanced heart failure, longer duration of heart failure, while the proportion of ischemic heart disease, diabetes and atrial fibrillation were higher in SwedeHF (all, $p < 0.001$) (Figure 8).

The three year survival rates were 83% (95% CI 80-85%) in SwedeHF vs. 61% (95%CI 54-67%) in TaHeF ($p < 0.001$; Figure 9).



Survival did not differ between HFpEF vs. HFrEF in either cohort (HFpEF vs. HFrEF $p=0.550$; SwedeHF HFpEF vs. HFrEF $p=0.108$). As in the overall population, survival in the matched population was worse in TaHeF than in SwedeHF (both in HFpEF and HFrEF $p<0.001$; HFrEF $p<0.001$; Figure 10).



Comparative prognosis and predictors of prognosis

In the matched cohort, the unadjusted risk of mortality was greater in TaHeF (HR 2.25 [95% CI 1.78-2.85], $p<0.001$), with three-year survival 61% vs. 83%. However, covariate-adjusted risk was similar (HR 1.07, 95% CI 0.69-1.66; $p=0.760$). In both cohorts, HFpEF was associated with higher mortality in crude but not adjusted analysis and variables associated with greater adjusted mortality included higher age and NYHA class (Table 7).

Table 7. Crude and adjusted risk of mortality in TaHeF vs. SwedeHF by Cox regression.		
	TaHeF vs. SwedeHF*	
Events/person-years	115/758 vs. 234/3995	
	Hazard ratio (95% CI)	p-value
Crude	2.25 (1.78-2.85)	<0.001
Multivariable model**	1.07 (0.69-1.66)	0.760
Adjusted for each of the following:		
NYHA class (2 categories) ^α	1.51 (1.17-1.95)	0.001
LVEF (4 categories) ^γ	2.17 (1.71-2.77)	<0.001
Caregiver unit (2 categories) ^β	2.64 (2.07-3.37)	<0.001
All 3 above (NYHA/LVEF/caregiver)	1.56 (1.17-2.06)	0.002
Educational level	1.96 (1.52-2.52)	<0.001
Duration of heart failure	1.95 (1.53-2.48)	<0.001
Ischaemic heart disease	2.69 (2.10-3.44)	<0.001
Hypertension	2.22 (1.75-2.81)	<0.001
Atrial fibrillation/flutter	2.71 (2.13-3.46)	<0.001
RAS	2.28 (1.80-2.88)	<0.001
Beta-blockers	2.02 (1.52-2.69)	<0.001
Aldosterone antagonist	1.93 (1.49-2.49)	<0.001
All 3 above (RAS/BB/Aldo)	1.78 (1.32-2.41)	<0.001
Heart rate	1.98 (1.53-2.55)	<0.001
Systolic blood pressure	2.31 (1.82-2.94)	<0.001
Body mass index (continuous, using restricted cubic splines)	2.06 (1.62-2.63)	<0.001
Creatinine clearance (continuous, using restricted cubic splines)	1.45 (1.14-1.85)	0.003
NYHA + creatinine clearance	1.08 (0.83-1.39)	0.585
*Reference category		
**Model was adjusted for NYHA, LVEF, heart failure duration, In/out-patient, Education, Smoking, Creatinine clearance, Systolic blood pressure, Heart rate, Body mass index, Ischemic heart disease, Atrial fib/flutter, Hypertension, Anemia, Diabetes, Lung disease, Calcific valve disease, RAS, Beta-blockers, aldosterone antagonist, Digoxin, Diuretics = 22 variables. (2 categories) ^α = I-II vs. III-IV, (4 categories) ^γ = LVEF<30 vs. 30-39,40-49, ≥50, (2 categories) ^β = Outpatient vs. inpatient		
CI = confidence interval		

STUDY IV

Figure 11 shows the flow of patients screened (n=237), included (n=102) and with completed follow-up (n=97).

Fifty-five patients (54%) were male and the mean age \pm SD 58 \pm 16 years. A majority of the patients had primary school education (54%). The heart failure etiology was hypertensive in 48%, dilated cardiomyopathy in 26%, ischemic in 15% and rheumatic heart disease in 7%. Renin angiotensin system antagonists, beta-blockers and mineralocorticoid receptor antagonists were used in 85%, 74% and 87% of the patients respectively.

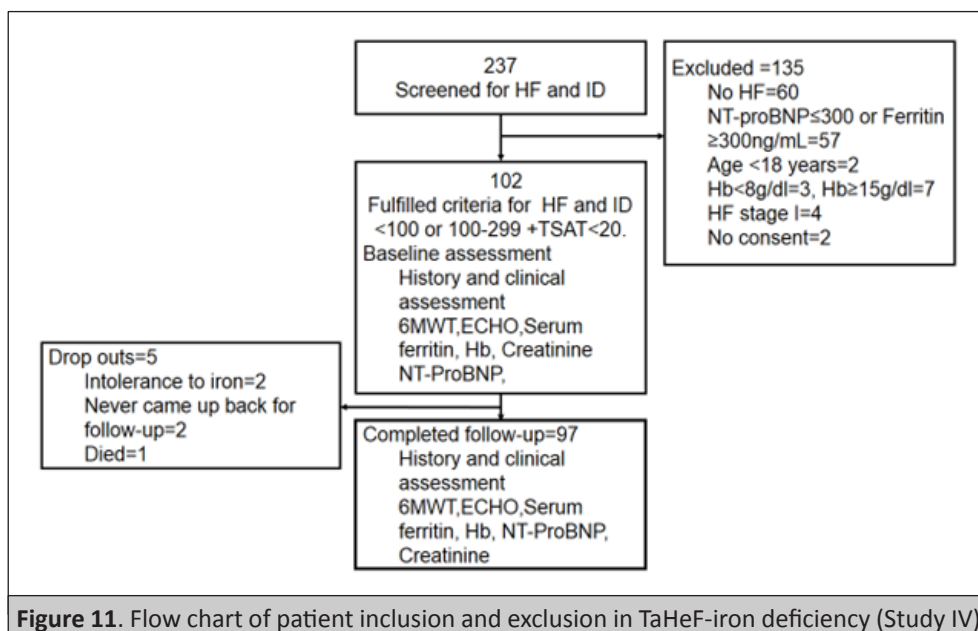
Primary endpoint

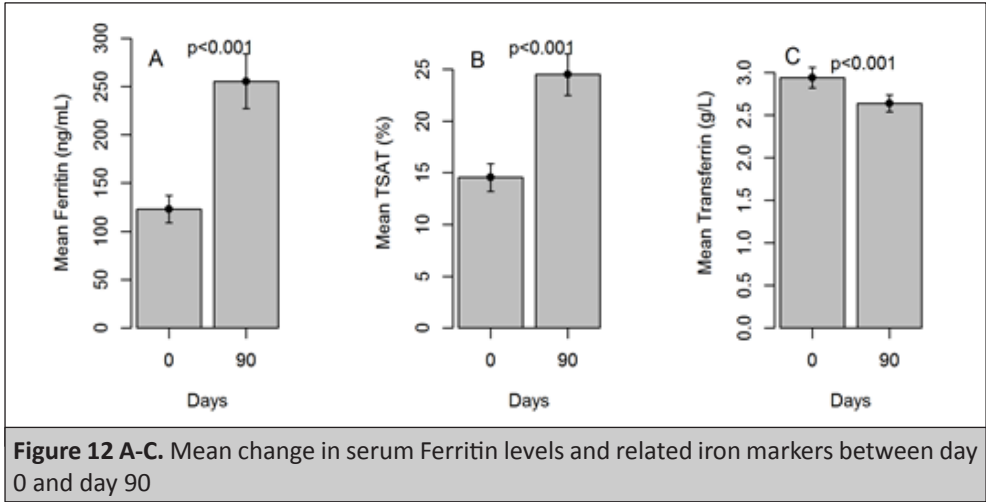
Five of the 102 patients did not complete 90 days of follow-up; out of these, 2 were intolerant to iron, 2 withdrew and 1 died. Thus 97 patients completed the study and were available for both baseline and follow-up assessment.

In the 97 patients, the ferritin level was 123 \pm 70 ng/mL at baseline and 255 \pm 143 ng/mL at day 90, a mean increase of 132 \pm 118 ng/mL (primary endpoint; +107%; $P<0.001$; Figure 12A). Numerous secondary endpoint parameters also demonstrated improvement. The corresponding values for TSAT were 10 \pm 12% at baseline and 25 \pm 10% after 90 days (+150%; $p<0.001$); transferrin 2.9 \pm 0.6g/L to 2.6 \pm 0.5g/L (-10%; $p<0.001$; Figure 12 B and C).

Primary and secondary endpoints

Secondary outcomes and other variables before and after oral iron are shown in Table 8.



**Table 8.** Secondary outcomes and other variables before and after oral iron (n=97).

Measure	Baseline	Day 90	Change		p-value
<i>Secondary endpoints</i>	Mean±SD	Mean±SD	Mean±SD	%	
Hemoglobin (g/dL)	11.7±2.0	12.3±1.8	0.6±1.4	5	<0.001
Creatinine clearance (mL/min)	61.2±27.9	63.8±33.2	2.6±18.7	4	0.1788
NT-proBNP (ng/L)	986.8±774.4	582.2±503.2	-404.7±452.6	-41	<0.001
LV ejection fraction (%)	37.8±12.2	44.5±10.7	6.6±9.8	17	<0.001
6MWT distance (meters)	543±148	574±166	31±67	6	<0.001
<i>Other variables</i>					
Serum iron (umol/L)	10.5±4.7	15.6±5.7	5.1±6.8	49	<0.001
Transferrin (g/L)	2.9±0.6	2.6±0.5	-0.3±0.6	-10	<0.001
White blood cells(x10 ⁹ /L)	6.2±3.0	6.1±2.1	-0.06±2.7	-0.9	0.826
Mean corpuscular volume (fl)	84.9±11.8	86.5±9.4	1.5±11.5	2	0.021
Mean corpuscular hemoglobin(pg)	27.5±4.4	29.2±3.0	1.7±3.4	6	<0.001
Mean corpuscular hemoglobin concentration (g/dL)	31.5±2.6	32.82±2.9	1.2±3.2	1	<0.001
Red cell distribution width (%)	17.5±3.7	15.9±2.5	-1.6±3.4	-9	<0.001
Platelets (nox10 ⁹ /L)	215.6±88.2	216.6±81.2	1.3±71.8	0.6	0.861

GENERAL DISCUSSION

Although there are previous studies of cardiovascular disease and heart failure in Sub-Saharan Africa^{17,19,20,34,111,112}, we believe the data presented in Studies I-IV are the most clinically detailed, up-to-date and comprehensive. In addition, Study III provides the first patient-level comparison between heart failure patients in a Sub-Saharan and a developed country.

The main findings in this thesis are 1) in Tanzania, as representative of Sub-Saharan Africa, heart failure patients are young with hypertension a major driving force and with anemia, iron deficiency and atrial fibrillation not treated with anticoagulation as common co-morbidities that are also associated with an impaired prognosis; 2) In heart failure in Tanzania, survival is worse compared to in Sweden, as representative of a developed country. However, after adjustment for the greater severity of heart failure in Tanzania and other differences between TaHeF and SwedeHF, the prognosis was similar; 3) oral iron supplementation was sufficiently absorbed to replenish iron stores in sub-Saharan patients with heart failure and iron deficiency. Accordingly, the present findings open for targeted public health interventions with the intention to impact the incidence and prognosis of heart failure in Tanzania and reasonably even other Sub-Saharan heart failure populations.

Demographics in heart failure

The findings that heart failure patients in Tanzania are younger than those in developed countries is of public health and societal importance as it impacts on an economically and a socially productive population. These patients are, in contrast to a majority of those in the developed world, in a productive age and may be caring for children. The TaHeF study along with a handful of other registries or cohort studies^{12,19,34} added to the volume of knowledge regarding heart failure demographics in Sub-Saharan Africa. The mean age of patients with heart failure in the USA and Europe is between 70-73 years^{113,114}. This contrasts greatly with the current findings and other studies in Sub-Saharan Africa, where the patients are between the ages of 42-59 years^{12,19,34}. One possible explanation for this difference is that hypertension, which according to Study I was an important main cause of heart failure in Tanzania, tends to affect patients already at a young and middle age¹¹⁵. In addition, they may have a more accelerated disease course more rapidly leading to end organ damage²¹. The disparity might also be explained by differences in life expectancy, which in 2014 averaged 63 years in Tanzania, 79 years in the US and 82 years in Sweden¹¹⁶.

In TaHeF, heart failure was almost equally distributed among males and females, consistent with the THESUS-HF. THESUS-HF was an observational survey of patients admitted with acute heart failure in nine countries of Sub-Saharan Africa whose goal was to describe causes, treatment and outcomes in heart failure¹². In the EHFS II, a study that examined clinical characteristics, etiology, treatment, and outcome of acute heart failure in Europe, patients were more commonly male (61%)¹¹⁷. Females were generally older than males in most of heart failure registries in developed countries^{117,118}, contrary to in TaHeF and THESUS-HF, in which males were slightly older. This might be explained by a higher life expectancy in females (84 years) than in males (80 years) in developed countries¹¹⁹, but the reasons why in Tanzania, male heart failure patients are older than female heart failure patients are less clear.

Etiologies of heart failure

TaHeF revealed that hypertension is a major etiological factor behind heart failure which is a striking temporal change in the historical pattern of heart failure in Tanzania and contrasts the dominant role of ischemic heart disease in developed economies^{120,121}. This finding in TaHeF outdates the previous predominance of rheumatic heart disease and cardiomyopathy as the major contributors to heart failure in Sub-Saharan Africa^{122,123} extending the findings from THESUS-HF^{12,19} and the Heart of Soweto Study Cohort¹⁹. Even after matching for age and in comparison to SwedeHF, the high rate of hypertension was consistent, calling for targeted and ambitious public health interventions to reduce the incidence of heart failure and possibly other complications of hypertension such as stroke, myocardial infarction and kidney disease. Several reports from Sub-Saharan Africa^{11,12,19} have emphasized hypertension as an increasingly important contributor to heart failure and other cardiovascular syndromes. These findings may reflect an ethnic characteristic with a genetic predisposition both to hypertension and to the adverse sequelae of hypertension potentially at an earlier stage than in Europeans^{11,21,111}. The higher rate of underdiagnosed, untreated, and inadequately treated hypertension in Sub-Saharan Africa than in developed countries might also explain this predominance of hypertension as a main risk factor in heart failure. Such risk may explain the considerably worse renal function that we observed in TaHeF and should encourage to early detection and target driven treatment according to available guidelines¹²⁴. Modifiable factors such as smoking, diet, and sedentary lifestyle, as well as under-diagnosis and under-treatment of hypertension, can be targeted at low cost and complexity.

The diminishing role of rheumatic heart disease and persistence of dilated cardiomyopathies (i.e. idiopathic and postpartum) in the TaHeF are consistent with findings from other Sub-Saharan Africa cohorts^{12,34}. Rheumatic heart disease is becoming less common in Sub-Saharan Africa in adults because of widespread use of antibiotics for group A streptococcal pharyngitis. Establishment of a national preventive program could possibly lead to further reductions of this condition, approaching the very low levels seen in developed countries.

Clinical presentation and comorbidities in heart failure

In the TaHeF study, patients presented late in the course of heart failure. This was reflected by findings from the matched TaHeF and SwedeHF cohorts, in which patients in Tanzania had clinically more severe heart failure by NYHA classification and worse renal function than those in Sweden. This may be attributed to patient delay and/or poor and/or later access to care. Even if access to care were adequate in Tanzania, the higher level of education in developed countries may be associated with higher health literacy and propensity to seek care than in Tanzania.

Anemia was common in heart failure despite the fact that a majority of patients were relatively young (median age 56 years), in a stable condition (49% in NYHA III as compared to 31% in NYHA IV) and ambulatory status (70% outpatients). The current findings (57% prevalence of anaemia) are about the same as in a similar study from Uganda³⁶ but in both this and the present study, the proportion was higher than in some other Sub-Saharan Africa countries (13-41%)^{45,46}. Compared to developed countries in which the anemia prevalence ranges from 21-33%, the prevalence in TaHeF was quite high, especially considering the about two decades higher age in such populations and that the prevalence of acute heart failure at study recruitment was higher in these countries^{41,42,61}. This may possibly be explained by high renal dysfunction and severity of heart failure, although these factors alone do not

seem to explain this large discrepancy in anemia prevalence. Like many other developing economies, Tanzania has a high prevalence of anemia among adults in the general population and thus the current findings maybe a reflection of this overall population structure in which the prevalence is 48%¹²⁵. Managing anemia, and in particular, iron deficiency, would also be of potential interest in attempts to improve symptoms prognosis in heart failure, provided that the beneficial effects of iron demonstrated in western countries^{52,87} are also applicable to patients with heart failure in Sub-Saharan Africa.

In contrast, other comorbidities such as diabetes, ischemic heart disease and atrial fibrillation were less common in TaHeF, as expected, as they presently reflect risk factors and disease patterns dominating in developed countries and with higher age. These findings may also be due to a relatively higher population prevalence of diabetes in Europe (9.6%)¹²⁶ and the USA (9.3%)¹²⁷ than in Tanzania (3.5%)¹²⁸.

HIV and Tuberculosis were found to be unique comorbidities seen in TaHeF, not being reported from most of the heart failure or cardiomyopathy cohorts in developed countries^{13,14,129} but mentioned in some¹³⁰. This pattern might be a true reflection of the population difference in which the prevalence of HIV in Africa is 4.4%, much higher than in Europe (0.4%)¹³¹. The contribution of HIV cardiomyopathy and TB pericarditis to the presumed cause of heart failure in about 3% of patients in TaHeF reflects the continuing impact of these conditions in Sub-Saharan Africa. The two conditions affect each other and HIV is associated with poor prognosis in heart failure^{130,132}.

Therapy

Regardless of underlying etiology, the heart failure syndrome is driven by compensatory but maladaptive neurohormonal activation. The neurohormonal hypothesis and the evidence based practice that evolved from randomized trials of neurohormonal antagonists represents a major advance in clinical medicine in general and heart failure in particular. Clinical trials such as Studies of Left Ventricular Dysfunction (SOLVD), the Metoprolol CR/XL Randomised Intervention Trial in-Congestive heart failure (MERIT-HF), the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II) trial, Randomized Aldactone Evaluation Study (RALES) and the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study^{23,24,133,134} have established ACE-inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists and beta-blockers as cornerstones in the treatment of heart failure with reduced ejection in developed countries. Fundamental heart failure therapy in the form of renin-angiotensin system inhibition (angiotensin-converting-enzyme inhibitor or angiotensin receptor blocker) was highly utilized in both TaHeF and SwedeHF, and spironolactone was used extensively in TaHeF. In fact, given the mild but worse renal function in TaHeF (median creatinine clearance 69 ml/min in this cohort, compared to 93 ml/min in the age and sex matched Swedish cohort), the use of RAS-antagonists was notably high but comparable to other cohorts in Sub-Saharan Africa^{20,34}. The high use of RAS-antagonists in TaHeF might be related to the belief that its survival benefit can be extended in even in those patients with heart failure and mild renal dysfunction. Indeed, data from the Heart Outcomes Prevention Evaluation (HOPE) study, the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Trial and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) studies have confirmed the benefit of angiotensin-converting-enzyme inhibitor use also in mild chronic kidney disease^{135–138}. The current patterns of use

of these drugs in TaHeF may be a reflection of improved adherence to guideline based heart failure therapy.

Despite these important practices, there is a need for additional studies on the efficacy of therapies for heart failure in black patients particularly in Sub-Saharan Africa due to reported lesser response to angiotensin-converting-enzyme inhibitor as compared to white patients^{139,140}. The findings from the African American Heart Failure (A-HEFT) trial¹⁴¹ that addition of a fixed dose of isosorbide dinitrate plus hydralazine to standard therapy for heart failure resulted in a better composite score made up of weighted values for death from any cause, a first hospitalization for heart failure, and change in the quality of life specifically among black patients with advanced heart failure should be further investigated in Sub-Saharan Africa trials.

In contrast, the low use of beta-blockers in TaHeF is concerning, and may reflect fear of worsening heart failure in patients with an already advanced heart failure syndrome (higher NYHA class). Digoxin and nitrates are readily available drugs historically used extensively in heart failure, and their greater use in TaHeF may reflect slower adoption of contemporary heart failure management.

Despite a not negligible 16% prevalence of atrial fibrillation in TaHeF, the use of oral anticoagulants was low, which is concerning with this arrhythmia already identified as an important risk marker of poor prognosis in heart failure. The 4% usage of warfarin in this population is low compared to in developed countries but also far below the 16% utilization reported from nine African countries as part of the Registry on variations in etiology and management of atrial fibrillation in a prospective (RE-LY AF) study¹⁴². This disparity might have resulted from the fact that the RE-LY AF included patients presenting in an emergency setting, suggesting a high-risk group, which could have prompted greater attention to indications for warfarin therapy, as well as the quality of care in RE-LY registry likely being positively affected by its connection with the trial itself.

With limited access to blood sampling for adjustment of warfarin-based anticoagulation and newer oral anti-coagulants remaining patented and expensive, atrial fibrillation, driven by hypertension and common in heart failure may indeed emerge as an important public health problem in Sub-Saharan Africa countries, whether in the presence or absence of heart failure. According to CHA₂DS₂-VASc score, heart failure provides one point, in itself resulting in an annual ischemic stroke of 0.6% risk of ischemic stroke in untreated patients¹⁴³, and heart failure frequently coexists with hypertension, higher age, and vascular disease, providing additional points and clear indications for oral anti-coagulation. Indeed, with anticoagulation the risk of ischemic stroke (and other embolic events) is reduced by about two-thirds irrespective of baseline risk^{144,145}. Thus ambitious public health interventions are required in Tanzania to reduce this risk by possibly providing continuing medical education to physicians, supply of anticoagulants, monitoring kits and adherence to the available treatment guidelines^{146,147}.

Despite a lack of efficacy evidence there was considerable use of most heart failure drugs also in heart failure preserved fraction in both TaHeF and SwedeHF. This may reflect the use of these drugs for hypertension or a perception that they may be effective in heart failure reduced ejection fraction.

Prognosis

After age and gender matching, the TaHeF patients had more than twice the crude risk of death compared to those in SwedeHF. As this greatly reflected more severe NYHA class and impaired renal function, and probably to some extent, less use of some evidence based heart failure drugs, there was no significant remaining difference in risk after multivariable adjustment. The few previous studies comparing heart failure in Sub-Saharan Africa vs. developed countries did not match patients or perform patient-level comparisons, nor did they perform adjustments for important confounders^{11,21,148}. Our findings suggest that previous data reflect a combination of younger age but greater severity of heart failure and less well developed treatment in Sub-Saharan Africa countries, with potentially opposite and balancing effects on outcomes.

Previous observations of similar prognosis in heart failure preserved vs. reduced ejection fraction^{149,150} were echoed in our study, which to the best of our knowledge is the first comparison of heart failure preserved vs. reduced ejection fraction in Sub-Saharan Africa and developed countries. Other studies, in particular clinical trials with selected and less representative patient populations, reported lower mortality in heart failure preserved ejection fraction^{110,151}.

Analysis of predictors of mortality in the TaHeF and SwedeHF populations revealed that the main predictors were similar. Exceptions were the lack of prediction by plasma sodium levels and of an association between the use of renin-angiotensin system antagonist and beta-blockers and outcomes. Although some of the predictors are similar to in THESUS-HF¹³², further exploration is needed, as the limited number of events in TaHeF may cause a type 2 statistical error.

Iron deficiency prevalence and association with prognosis in heart failure

A specific and highly relevant comorbidity in heart failure is iron deficiency, which is common and associated with increased risk whether associated with anemia or not. Iron deficiency was examined in studies II and IV. The overall prevalence of iron deficiency regardless of anemia was 49%. This is comparable to findings reported from pooled analyses from developed countries⁷⁷. The prevalence was higher in the TaHeF population than the 22% and 37% reported in some studies^{74,89}, but lower than reported in others^{61,75,76} in which iron deficiency was seen in 58-73%.

Data on the epidemiology and pathophysiology of iron deficiency in heart failure in Sub-Saharan Africa are scarce. The variations in iron deficiency prevalence seen in the above studies might relate to a lack of standard definitions for iron deficiency in heart failure and differences in the characteristics of the studied populations. Underlying malnutrition and chronic infections, less commonly seen in developed countries, are other potential contributors in developing countries.

The relation between iron deficiency, anemia and heart failure has been explored in developed countries⁸⁹. Recent reports indicate that iron deficiency is associated with a compromised prognosis in heart failure, which is independent of anemia^{77,89}. Considerably less is known about the role of iron deficiency and anemia in heart failure populations from Sub-Saharan Africa⁵⁰.

There are limited data reporting the impact of iron deficiency on prognosis in heart failure. There are conflicting findings though poor outcome appears to be the predominant finding. In most available studies^{74,76,77,89}, iron deficiency carried a higher risk of poor outcome in heart failure irrespective of the presence of anemia. In contrast, Parikh et al⁷⁵ found that iron deficiency did not relate to all cause or cardiovascular mortality in patients with self-reported heart failure. The present data show that iron deficiency anemia but not anemia or iron deficiency alone was an independent predictor of poor outcomes in heart failure. Four statistical models were analyzed taking into consideration both iron deficiency and anemia and including both patients with heart failure preserved and reduced ejection fraction. It appeared that not only anemia or iron deficiency alone but more importantly iron deficiency anemia was associated with the worst prognosis in heart failure. Further studies in heart failure are needed to explain the prognostic variations and levels of impact contributed by each of iron deficiency, iron deficiency and anemia alone and in combination.

Iron therapy in heart failure

Study IV demonstrated for the first time that oral iron improves serum ferritin levels in patients with heart failure and iron deficiency in a prospective study design setting. Serum ferritin more than doubled after the administration of oral iron during 90 days in patients with heart failure, providing evidence of a preserved or at least adequate bioavailability of oral iron in such populations. That oral iron is able to increase ferritin levels suggests that it has been absorbed through the gastrointestinal tract. Thus the purported inhibition of oral absorption by hepcidin modulation at the gastrointestinal level remains controversial, particularly in patients with heart failure^{51,62}.

The magnitude of the incremental increase in ferritin in the current study was slightly higher than the 98% reported by Niehaus et al. in retrospective study of 105 patients with heart failure reduced ejection fraction¹⁰⁶. This may at least partially be explained by different study designs (retrospective vs. prospective) allowing a closer monitoring of adherence in the current study. In comparison to randomized trials which applied oral iron in one of their arms, a serum ferritin incremental increase was consistent in the present study with the findings reported by Beck-da Silva et al¹⁰⁷ in the oral iron arm and better than in Parissis et al¹⁵². The possibility to compare the present findings with studies administering iron intravenously in patients with heart failure^{96,97} is limited due to substantial methodological differences. Findings in the i.v. iron arm of the FAIR-HF⁸⁶ appear similar to the current data. Thus, study IV suggests that iron stores may be recovered with oral iron to a similar extent as with i.v. iron. If confirmed these findings may have considerable beneficial logistical and practical implications.

Previous studies in heart failure have not shown an improvement in exercise capacity with oral iron^{152–154}, whereas one small study in cyanotic congenital heart disease has¹⁵⁵. The present improvement in 6MWT, +31 meters or 6% after 90 days of oral iron, is comparable to the +30–40 meters compared to placebo by i.v. iron in the Ferinject Assessment in Patients with IRon deficiency and chronic Heart Failure (FAIR-HF)⁸⁶ and Ferric CarboxymaltOse evaluation on perFormance in patients with IRon deficiency in coMbination with chronic heart failure (CONFIRM-HF)^{86,87}. A major appeal of i.v. iron is the large and consistent improvement in peak VO₂⁸⁸, as well as 6MWT distance, NYHA class, and quality of life measured by EQ-5D and the Kansas City Cardiomyopathy Questionnaire (KCCQ)^{52,87}. However, the

costs and logistical challenges of i.v. iron treatment in large heart failure populations may complicate its implementation particularly in countries with limited health care resources. Thus oral iron should be extensively studied particularly in Sub-Saharan Africa, where both the resources of i.v. iron and the pathophysiology of iron deficiency may be different from that in developed countries. Although study IV provided distinctly positive findings, due to absent randomization it is not possible to rule out a placebo effect, particularly on the 6MWT. Therefore, it is important to verify the present findings in a randomized trial.

Limitations of the studies presented in this thesis

The TaHeF study was conducted in a developing country where resources for recruitment, diagnosis, monitoring of patients and embarking on clinical trials are limited. If further patients could have been recruited it would have contributed to more events. By similar reasons, a non-randomized clinical trial (study IV) was the first feasible step prior to more complex and expensive randomized trials.

Policy implications and considerations

- The findings in Studies I-IV are highly clinically and socially relevant. They may be addressed with quite simple and inexpensive measures.
 - Hypertension emerged to be a predominant contemporary cause of heart failure in Sub-Saharan Africa. Hypertension is easy to diagnose and treat. The findings in this thesis thus call for concerted policy efforts to improve awareness of hypertension and access to diagnosis and therapy on a population level.
 - Anemia, iron deficiency, atrial fibrillation, and lower education level adversely impacted the prognosis of heart failure. In this context, the underutilization of oral anti-coagulation in Tanzania in the setting of heart failure and atrial fibrillation is concerning and highlights the need for improved access to oral anti-coagulation therapy and monitoring. Novel approaches to treating anemia and iron deficiency, such as potentially oral iron, are needed. Broadening access to education may improve health literacy and health outcomes in general.

CONCLUSIONS

Patients with heart failure in Tanzania are younger than in developed countries but the etiologies are becoming more similar, with hypertension becoming more and rheumatic heart disease less important. Even after age and gender matching (vs. heart failure patients in Sweden), patients in Tanzania had more severe heart failure despite higher LVEF, and worse crude but similar adjusted prognosis. Hypertension was a common risk factor and underlying etiology and is possible to screen for and treat. Predictors of mortality possible to intervene against were anemia, atrial fibrillation and lack of education. Iron deficiency was common in heart failure patients in Tanzania and was independently associated with the risk for heart failure hospitalization or death. Oral iron supplementation was sufficiently absorbed to replenish iron stores in Sub-Saharan patients with heart failure and resulted in improved hemoglobin, 6MWT distance, LVEF and NT-proBNP.

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